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Microbiologic testing for meningitis, encephalitis, and meningoencephalitis

Etiology	Preferred testing method(s) when clinically suspected and role of NAT
Bacteria	
Common pathogens (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*)	Gram stain and bacterial culture Include CSF NAT for: ▪ Gram stain positive, culture negative ▪ Clinical suspicion for bacterial meningitis with antibacterial therapy prior to CSF collection ▪ No culture available, only cell count Consider CSF amplicon sequencing in cases with negative culture and targeted NAT but persistent suspicion for infection and microorganisms by microscopy
Fastidious organisms (*Mycoplasma* spp, *Tropheryma* spp, *Brucella* spp, *Bartonella* spp)	Serology; include CSF NAT when suspected clinically
Listeria spp	Bacterial culture; include CSF NAT in neonates, elderly, and immunocompromised with meningitis/meningoencephalitis
*Mycobacterium tuberculosis**	AFB stain, AFB culture; include CSF NAT in cases with high clinical suspicion
Coxiella burnetii	Serology; include CSF NAT when suspected clinically
Viruses	
Adenoviruses	Respiratory specimen NAT is preferred CSF NAT is rarely indicated and low yield

Arboviruses (including West Nile virus)[¶]	CSF and serum antibodies (especially CSF IgM) Include CSF NAT (in addition to antibody testing) in rare cases (eg, when suspected clinically in patient at risk for poor antibody response)
Cytomegalovirus (CMV)	CSF NAT[Δ]; use quantitative CSF NAT when CMV-related CNS infection is suspected clinically (eg, to investigate positive qualitative CSF CMV NAT in patient with risk factors and clinical suspicion of CMV-related CNS infection)
Epstein Barr Virus (EBV)	Serum antibody panel; limit CSF NAT (preferably quantitative) to patients with risk factors and suspicion of EBV-related CNS disease
Enteroviruses	CSF NAT
Human herpesvirus 6 (HHV-6)	CSF NAT[Δ], use quantitative CSF NAT (± other tests) to distinguish active HHV-6 CNS infection from chromosomal integration or latent infection when suspected clinically
Herpes simplex virus (HSV)	CSF NAT; consider performing a high-sensitivity singleplex NAT in patients with negative multiplex panel and high clinical suspicion
Influenza	Respiratory specimen NAT is preferred CSF NAT is rarely indicated and low yield
Lymphocytic choriomeningitis virus	CSF and serum antibodies; CSF NAT when suspected clinically
Mumps	Viral culture, serology, and NAT from buccal mucosa CSF NAT is rarely indicated but may be available from public health laboratories in high suspicion cases
Parechoviruses[◇]	CSF NAT (include primarily in children <5 years old)
Rabies	Refer to UpToDate text; rabies testing is limited to public health laboratories and requires multiple specimen types (serum, saliva, nuchal skin biopsy, CSF) and multiple tests (serology, histology with special stains, NAT)
Varicella-zoster virus	CSF NAT (plus CSF antibodies in select cases)[§]
Rickettsia[¥]	Serology CSF NAT has limited availability
Spirochetes	

Leptospira	Serology CSF NAT is rarely indicated and not routinely available
Borrelia burgdorferi (the agent of Lyme disease)	Serology including CSF and serum IgG index CSF NAT is not indicated
Treponema pallidum (syphilis)	Serology, CSF VDRL CSF NAT is not indicated
Fungal	
Cryptococcus spp	CSF ± serum antigen detection (CrAg), fungal culture; consider high-sensitivity CrAg testing in patients with clinical suspicion for cryptococcal meningitis and negative CSF NAT (ie, negative multiplex NAT panel)
Dimorphic fungi (*Coccidioides* spp, *Histoplasma* spp, rarely *Blastomyces* spp)	Serology, CSF antibody and antigen testing (eg, (1,3) Beta-D-Glucan antigen immunoassay), and fungal culture when suspected clinically NAT is rarely indicated
Other molds	Fungal culture For suspected invasive fungal infection (eg, invasive aspergillosis), consider amplicon sequencing of infected tissue when microorganisms are visible by microscopy (fungal hyphae) and culture negative or not performed
Parasites	
Toxoplasma gondii	Serology, CSF NAT
Microsporidia	Serology, stains, histologic exam NAT availability is limited and rarely indicated
Free-living amebae (eg, *Naegleria fowleri*)	CSF wet mount; NAT when suspected clinically NAT availability is limited to public health and referral laboratories
Human African trypanosomiasis	Serology, direct examination, CSF antibody NAT not available

Angiostrongylus cantonensis, Gnathostoma spinigerum, Baylisascaris procyonis	Serology, direct examination; NAT when suspected clinically (eg, risk factors + CSF eosinophilia) NAT availability is limited
Other parasites (*Balamuthia mandrillaris*)	Histologic exam; serology and NAT when suspected clinically NAT availability is limited to public health and referral laboratories
Severe disease with unknown etiology after initial laboratory investigations	Primary test: Metagenomic sequencing of CSF from initial lumbar puncture specimen (frozen saved specimen, ideally pretreatment) Secondary test for use in select cases only: Metagenomic sequencing of EDTA plasma from day 1 or 2 of hospitalization (frozen saved specimen, ideally pretreatment) May be particularly useful for: ▪ Immunocompromised individuals ▪ Extensive travel history ▪ Detection of unusual viruses and pathogens

AFB: acid-fast bacilli; CrAg: cryptococcal antigen; CSF: cerebrospinal fluid; EDTA: ethylenediaminetetraacetic acid; Ig: immunoglobulin; NAT: nucleic acid testing; PPV: positive predictive value; VDRL: Venereal Disease Research Laboratories; VZV: varicella-zoster virus.

* Variable sensitivity, high PPV, rapid.

¶ Virus is usually cleared rapidly and early from blood and CSF prior to symptom onset except for immunocompromised individuals.

Δ Interpret positive tests with caution, may not be clinically relevant.

◇ Not detected by most enterovirus assays.

§ CSF serology should be performed when clinical suspicion for varicella-zoster virus is high and the presentation is subacute (eg, VZV vasculopathy or onset of CNS symptoms following recent episode of zoster).

¥ Limited experience from CSF.

Graphic 58078 Version 10.0